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Original Article

HIV, vascular surgery and cardiovascular outcomes: a South African cohort study

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Summary

Risk factors for peri-operative cardiac morbidity are poorly described in HIV-positive patients. This prospective observational study describes cardiovascular risk factors in a cohort of vascular surgical patients of known HIV status. We recruited 225 patients with 73 (32%) being HIV-positive. When compared with HIV-negative patients, the HIV-positive patients were younger (mean (SD) 56.4 (13.3) vs 40.5 (10.4) years, respectively, $p < 0.01$). They had fewer Revised Cardiac Risk Index cardiovascular risk factors (median (range [IQR]) 1 (0–5 [0–2]) vs 0 (0–2 [0–0]), respectively, $p < 0.001$), with the exception of congestive cardiac failure ($p = 0.23$) and renal dysfunction ($p = 0.32$), and so were of a significantly lower Revised Cardiac Risk Index risk category ($p < 0.01$). HIV-positive and -negative patients had similar outcomes in: 30-day mortality ($p = 0.78$); three-day postoperative troponin leak ($p = 0.66$); and a composite outcome of mortality and troponin release ($p = 0.69$). We conclude that although HIV-positive patients have fewer cardiovascular risk factors, they have similar peri-operative major adverse cardiac events to HIV-negative patients. Research should focus on why this is the case, and if alternative clinical risk predictors can be developed for HIV patients.

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Introduction

The human immunodeficiency virus (HIV) epidemic is increasing worldwide and in 2010, the total number of HIV-positive people in South Africa alone totalled > 5 million or ~1/6 of the world's HIV-positive population [1]. HIV vasculopathy is a poorly understood disease with generally poor outcomes. These include high rates of morbidity, mortality and poor limb salvage in young patients [2, 3]. There are few studies that consider the cardiovascular risk profile of HIV-positive vascular patients [2, 4] and we are unaware of any data on cardiovascular outcomes in HIV-positive patients following vascular surgery, or whether specific cardiovascular risk factors are important for risk stratification. The importance of the pre-operative CD4 count for risk stratification is controversial, and a single study suggests that hypoalbuminaemia may be important [3, 5]. Furthermore, there is no consensus as to the optimal medical and surgical management of these patients.

A prospective observational study of vascular surgical patients in Kwazulu-Natal South Africa studied

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clinical risk factors associated with major adverse cardiac events (MACE) [6]. This current study presents the data of the HIV subpopulation of that cohort. Our aim was to describe the clinical characteristics, risk factors and outcomes associated with HIV in vascular surgical patients. The primary outcome of this study was postoperative cardiovascular morbidity in HIV-positive patients following vascular surgery.

Methods

A prospective cohort study of cardiovascular risk factors and associated peri-operative cardiac morbidity in elective vascular surgical patients was conducted at Inkosi Albert Luthuli Central Hospital, in KwaZulu-Natal, South Africa. Local ethics approval was obtained. We recruited vascular surgical patients between February 2008 and March 2011. The methodology of the study has previously been published [6]. All elective vascular surgical patients between 19 February 2008 and 15 March 2011 were eligible for recruitment into this prospective observational cohort study. After signed informed consent, patients had troponins measured daily for the first three postoperative days as part of the study outcome. Patients could consent to (1) the collection of clinical risk factors only, or (2) clinical risk factors with pre-operative biomarker collection, or (3) clinical risk factors, pre-operative biomarkers and ambulatory Holter monitoring, and (4) pre-operative HIV testing.

In total, 978 patients were eligible for the study, of whom 788 consented to the full study. This HIV study is a substudy of the original full study. It consists of the 225 patients who also consented to HIV testing from the original 788 patient cohort. All 225 patients were previously reported as part of the entire cohort in the original publication [6]. We have presented these HIV data separately to the original publication, as the data analysis and findings are sufficiently different from the entire vascular surgical group to warrant a separate full publication to present the data.

HIV testing was performed using the ELISA testing method of a formal blood sample in an automated Roche E160 analyser. A potentially positive sample was confirmed with a second ELISA run in a second automated Centaur analyser.

All clinical risk factors were prospectively collected. The definitions used in the derivation of the Revised Cardiac Risk Index [7] were used in this study. The primary outcome was postoperative MACE. This was defined as a serum troponin level above the laboratory upper reference limit within the first three postoperative days and/or death within the first 30 postoperative days.

All categorical data were analysed using descriptive statistics and analysed using Fisher's exact test or Pearson's chi-squared test where appropriate. All continuous data were analysed using descriptive statistics and compared using independent samples t-test or Mann–Whitney U-test, with $p < 0.05$ indicating statistical significance.

Results

Patients' eligibility and recruitment are shown in Fig. 1. The HIV substudy consists of 225 consenting patients. Within this cohort, 73 patients (32%) tested positive for infection.

The patients' characteristics, cardiovascular risk factors, pre-operative medical therapy and vascular surgical procedures are shown in Table 1. Compared with the HIV-negative patients, HIV-positive patients were significantly younger, had fewer cardiovascular risk factors (i.e. a history of hypertension, ischaemic heart disease, diabetes and cerebrovascular accidents)

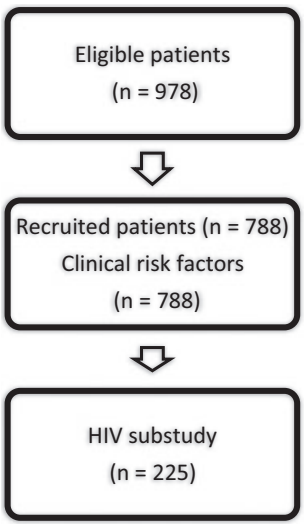

Figure 1 Flow diagram of study and patient recruitment.

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Table 1 Pre-operative patients' characteristics, cardiovascular risk factors, cardiac medications and vascular surgical procedures. Values are mean (SD) or number (proportion).

	Total (n = 225)	HIV-negative (n = 152)	HIV-positive (n = 73)	p value
Age; years	51.2 (14.5)	56.4 (13.3)	40.5 (10.4)	0.001
Male	155 (69%)	99 (65%)	56 (77%)	0.91
IHD	48 (21%)	43 (28%)	5 (7%)	< 0.01
CHF	12 (5%)	10 (7%)	2 (3%)	0.23
CVA	42 (18.7%)	36 (23.7%)	6 (8.2%)	< 0.01
DM	61 (27.1%)	56 (36.8%)	5 (6.8%)	< 0.01
Creatinine > 177 $\mu mol.l^{-1}$	7 (3.4%)*	6 (4.3%)†	1 (1.5%)‡	0.32
Hypertension	133 (59%)	109 (72%)	24 (33%)	< 0.01
Smoker	163 (72%)	108 (71%)	55 (75%)	0.53
Revised Cardiac Risk Index classification [7]				
Low risk (0 risk factors)	109 (53%)	58 (41%)	51 (79%)	< 0.001
Intermediate risk (1–2 risk factors)	81 (39%)	67 (48%)	14 (22%)	
High risk (≥ 3 risk factors)	16 (8%)	16 (11%)	0	
Pre-operative cardiovascular medications				
β-Blockers	63 (28%)	53 (35%)	10 (14%)	< 0.01
Statins	177 (79%)	133 (88%)	44 (60%)	< 0.01
Aspirin	195 (87%)	137 (90%)	58 (80%)	0.04
Vascular surgical procedures				
Thoraco-abdominal aortic aneurysm repair	1 (0.4%)	0	1 (1.4%)	0.02
Abdominal aortic aneurysm repair	10 (4.4%)	7 (4.6%)	3 (4.1%)	
Aorto-bifemoral bypass graft	15 (6.7%)	12 (7.9%)	3 (4.1%)	
Axillo-femoral bypass graft	3 (6.7%)	3 (2%)	0	
EVAR	11 (4.9%)	9 (5.9%)	2 (2.7%)	
Carotid endarterectomy	17 (7.6%)	17 (11.2%)	0	
Carotid stent	19 (8.4%)	14 (9.2%)	5 (6.8%)	
Infra-inguinal bypass surgery	82 (36.4%)	53 (34.9%)	29 (39.7%)	
Amputation	22 (9.8%)	11 (7.2%)	11 (15.1%)	
Other	45 (20%)	26 (17.1%)	19 (26%)	

*n = 206.
†n = 141.
‡n = 65.
IHD, ischaemic heart disease; CHF, congestive heart failure; CVA, cerebrovascular accident; DM, diabetes mellitus; EVAR, endovascular aortic aneurysm repair.

and a lower Revised Cardiac Risk Index [7]. Only a history of congestive cardiac failure (p = 0.23), smoking (p = 0.53) and renal dysfunction, defined as a serum creatinine > 177 $\mu mol.l^{-1}$ (p = 0.32), were similar between HIV-positive and -negative patients. The HIV-positive patients received significantly fewer cardiac medications before vascular surgery. The vascular surgical procedures differed between HIV-positive and -negative patients. No carotid endarterectomies were performed on HIV-positive patients, and amputation was double that of HIV-negative patients.

Patients' outcomes are shown in Table 2. There was no significant difference in the incidence of postoperative troponin leak, 30-day mortality or MACE between the HIV-positive and -negative patients. Within the HIV cohort, patients who suffered MACE were more likely to be younger, female, have a history of diabetes and receive β-blockers pre-operatively (Table 3).

Sixty-two patients had CD4 counts recorded with a mean (SD) of 331 (211) $cells.mm^{-3}$. Twenty-one (29%) patients had AIDS defining levels of CD4 cell count of < 200 $cells.mm^{-3}$. Median (IQR [range]) CD4 count was not significantly different (p = 0.30) between the HIV-positive patients who did (256 (121–352 [112–446])) $cells.mm^{-3}$ or did not (304 (163–456 [36–1158])) $cells.mm^{-3}$ suffer the primary composite outcome of MACE within 30 days postoperatively.

Twenty-three of the HIV-positive patients were on anti-retroviral therapy (ART), although 36 were eligible. There was no statistical association between ART and MACE (9% with ART vs 18% without ART, p = 0.3).

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Table 2 Major adverse cardiac events following vascular surgery. Values are number (proportion).

	Total (n = 225)	HIV-negative (n = 152)	HIV-positive (n = 73)	p value
Postoperative troponin leak	26 (12%)	19 (13%)	7 (10%)	0.66
Died < 30 days	11 (5%)	7 (5%)	4 (6%)	0.78
MACE	31 (14%)	20 (13%)	11 (15%)	0.69

MACE, major adverse cardiac events defined as a troponin leak above the laboratory reference limit within the first three postoperative days and/or death within 30 days of surgery.

Table 3 Pre-operative HIV-positive patients' characteristics, cardiovascular risk factors and cardiac medications. Values are mean (SD) or number (proportion).

	MACE present (n = 11)	MACE absent (n = 62)	p value
Age; years	37.6 (10.4)	40.1 (10.3)	0.03
Male	5 (46%)	51 (82%)	< 0.01
IHD	1 (9.1%)	4 (6.5%)	0.75
CHF	0	2 (3.2%)	0.55
CVA	1 (9.1%)	5 (8.1%)	0.91
DM	3 (27.3%)	2 (3.2%)	< 0.01
Creatinine > 177 μmol.l^{-1}	0†	1 (1.8%)‡	0.67
Hypertension	3 (27%)	21 (34%)	0.67
Smoker	6 (54.5%)	49 (79%)	0.08
Revised Cardiac Risk Index classification			
Low risk	6 (60%)	45 (82%)	0.15
Intermediate risk	4 (40%)	8 (15%)	
High risk	0	2 (3.6%)	
Pre-operative cardiovascular medications			
β-Blockers	4 (36%)	6 (9.7%)	0.02
Statins	7 (64%)	37 (60%)	0.81
Aspirin	10 (91%)	48 (77%)	0.31

†n = 10.
‡n = 55.
MACE, major adverse cardiac events dened as a troponin leak above the laboratory reference limit within the first three postoperative days and/or death within 30 days of surgery; IHD, ischaemic heart disease; CHF, congestive heart failure; CVA, cerebrovascular accident; DM, diabetes mellitus. In the Revised Cardiac Risk Index (from ref [7]) the risk factors are: Low (0); Low (1–2); High (>3).

Discussion

The main finding of this observational study is that although HIV-positive vascular patients are significantly younger and carry fewer cardiovascular risk factors than the typical vascular patient, they have a similar composite outcome of death and troponin leak following vascular surgery when compared with HIV-negative vascular patients.

The recent Vascular events In non-cardiac Surgery patIents cOhort evaluatioN (VISION) study has shown that a positive troponin leak has the highest population attributable risk for 30-day mortality following non-cardiac surgery, when compared with other independent pre-operative risk factors [8]. In our cohort, the HIV-positive patients had a similar incidence of MACE and troponin leak, yet the HIV-positive patients received significantly fewer pre-operative cardiovascular medications potentially protective against a troponin leak, probably secondary to fewer cardiovascular risk factors and the younger age of the HIV-positive patients. Unfortunately, this too may impact on the survival of the HIV-positive patients, as currently, the only observational evidence suggests that a potential survival advantage following a postoperative troponin leak is the administration of statin and aspirin at the time of this troponin leak [9]. Our data suggest that HIV-positive patients presenting for vascular surgery are at similar cardiovascular risk to traditional arteriopaths, and should therefore probably receive similar cardioprotective medications.

This study suggests that a large prospective observational cohort study is needed to determine appropriate risk factors for postoperative MACE in HIV-positive patients. Our study suggests that the cardiovascular risk factors used to risk stratify traditional arteriopaths may be inappropriate for cardiac risk stratification in HIV-positive patients. Furthermore, more aggressive cardiovascular medication may be necessary to prevent postoperative cardiac morbidity in HIV-positive patients even in the absence of traditional cardiovascular risk factors. Both statins and β-blockers have been associated with cardiovascular protection in the perioperative period [10, 11].

The characteristics of our HIV-positive patient cohort confirm some of the existing knowledge and highlight some of the areas requiring further investigation. HIV has a higher prevalence among females with the exception of vascular surgical patients where males predominate [3], as in our HIV cohort. However, the

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female HIV-positive patients suffered significantly more postoperative cardiovascular morbidity than male patients. The reason for this observation remains unclear.

A recent review suggests that HIV-positive patients should have a similar surgical outcome to HIV-negative patients [12]. Previous surgical reports have shown a higher morbidity and mortality in HIV-positive patients when compared with HIV-negative patients. However, when the HIV-positive patients were compared with other immunocompromised patients (e.g. advanced age, diabetes, radiotherapy, etc.), their outcomes were similar [12]. Thus, the consensus is that HIV-positive patients should not be excluded from surgery unless they have an AIDS-defining condition or are too physiologically unfit [12]. However, we find that a note of caution is warranted: had these patients been pre-operatively risk stratified using the Revised Cardiac Risk Index [7, 13] as suggested by guidelines [13, 14], they would have had been considered at significantly lower cardiac risk than they actually are, and the expected postoperative cardiac morbidity would have been lower than that observed. It would appear, therefore, that either the Revised Cardiac Risk Index [7] is an inappropriate risk stratification tool for HIV-positive vascular surgical patients, or that being HIV-positive needs to be factored into existing scores to adjust for this. Another important observation from our data is that the physiological age advantage of HIV-positive patients does not appear to improve their peri-operative outcome.

Initiation of treatment for HIV has been associated with an increase in survival and patients may have a near-normal life expectancy. Treatment should therefore be initiated in a timely manner and compliance ensured [14]. It would be important to address the efficacy of ART in improving postoperative outcome in vascular patients, and whether AIDS-defining illness is associated with a significantly worse outcome in vascular surgical patients. Previous studies suggest that a CD4 count of < 50 cells.mm^{-3} is associated with increased surgical morbidity and decreased long-term survival [12]. A CD4 < 200 cells.mm^{-3} has been associated with decreased long-term survival following aortic vascular surgery [5]. The CD4 count was similar between patients with and without MACE in our cohort, and both of the two patients who had a CD4 count < 50 cells.mm^{-3} did not suffer MACE.

Patients who were on ART were not protected from vascular disease. The efficacy of ART is more difficult to assess in vascular patients as there are adverse vascular side-effects associated with ART (e.g. metabolic syndrome). Thus, while opportunistic infections may be reduced and life expectancy increased, the vascular complications may actually be aggravated by the treatment [15]. Conversely, as HIV is characterised by a leucocytoclastic vasculitis, statin therapy may be theoretically beneficial in these patients [4].

There are other limitations associated with this study. First, we present a heterogeneous group of vascular surgical procedures (Table 1) and we are unable to analyse outcomes with sufficient statistical power in specific vascular surgical risk groups, e.g. carotid surgery, peripheral bypass surgery and aortic aneurysmal surgery, etc. [16]. Furthermore, we did not capture data on the functional status of the patients. HIV is commonly associated with cardiomyopathy [17]. It is possible that this may have been associated with both poor cardiovascular outcomes and limb patency.

Second, we did not routinely screen postoperative ECGs for ischaemic changes or echocardiography for regional wall motion abnormalities, and hence a diagnosis of myocardial infarction was not made. We believe that our definition of MACE is, however, valid, as this definition was first adopted in 2005 [18] and subsequently, a postoperative troponin leak has been shown to be the strongest independent predictor of 30-day MACE [8] and its utility has been subsequently confirmed in a separate study [19]. Importantly, should traditional myocardial infarction criteria be adopted, a large proportion of prognostically important troponin releases are missed (97% in the most recent publication) [19].

A final limitation of this study is that this HIV-positive vascular surgical population is relatively young, which is consistent with other South African data [2]. However, it is expected that HIV-positive vascular surgical patients in a developed world setting would be older than South African HIV cohorts [5]. It is therefore possible that cardiovascular risk factors may be important in HIV-positive vascular surgical

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populations where the patient population is older than that reported in this study.

In conclusion, although HIV-positive vasculopaths are young with generally fewer cardiovascular risk factors, surgery is associated with significant peri-operative cardiac morbidity. Interventions to decrease cardiovascular morbidity should be considered in these patients, such as optimisation of cardiovascular medical therapy, which may improve cardiovascular outcomes. Furthermore, postoperative troponin surveillance should be considered for all these patients to identify and manage high-risk cases. The role of other risk stratification tools needs further evaluation, and the importance of CD4 counts and ART on early postoperative outcomes remains unclear.

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Competing interests

No other funding or competing interests declared.

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